with any therapeutic candidate development paradigm, toxicologic and safety pharmacology evaluations should indicate a low level of risk associated with dosing and administration procedures, thereby enhancing the rationale for investing in such a modality for the treatment of OA.

I-3
IMPACT OF KNEE OA ON MEETING PHYSICAL ACTIVITY GUIDELINES

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Purpose: Physical activity has irrefutable health benefits. For people with knee osteoarthritis (OA), pain is a well-known cause of functional limitation in people with knee (OA), however it is unclear whether it is also responsible for a reduction in physical activity behaviors. Anecdotally, pain is thought to be responsible for less physical activity. We will review the literature investigating whether knee OA-related pain is in fact a risk factor for less physical activity. As well, we will investigate whether physical activity is responsible for changes in pain.
Methods: We will summarize studies of objectively measured physical activity among people with knee OA from well-established cohort studies. We will also review the association of physical activity with knee pain and function from clinical intervention trials and observational studies among people with knee OA.
Results: Physical activity guidelines, i.e., participation in at least 150 minutes of moderate to vigorous physical activity (MVPA), was met by 12.9% of men and 7.7% of women from the Osteoarthritis initiative. However, a similarly low proportion met guidelines from the National Health and Nutrition Examination Survey. Furthermore, a similar proportion of people with and without knee pain met guidelines from daily walking from the Multicenter Osteoarthritis (MOST) study. These data suggest the presence of knee pain may not fully account for low levels of physical activity in knee OA. Clinical trials incorporating physical activity interventions, such as aerobic walking, reduce knee pain. We have previously reported a strong association between walking at least 6,000 steps/day and the prevention of functional limitation 2 years later in the MOST study.
Conclusions: Knee pain alone may not lead to a reduction in physical activity among people with knee OA. However, the benefits of adopting a physically active lifestyle include reducing existing knee pain and preventing the development of functional limitation in knee OA.

I-4
THE AGING PROCESS AND EPIGENETICS: RELATIONSHIP WITH OA

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Purpose: The term 'epigenetics' refers to heritable changes in gene expression or phenotype that occur without changes to the underlying DNA sequence. There are three mechanisms of epigenetic gene regulation; DNA methylation, post-translational modifications of histone proteins, and non-coding RNAs (ncRNAs) such as microRNAs. They regulate gene expression either by affecting gene transcription (DNA methylation, histone modifications and some ncRNAs) or by acting post-transcriptionally, leading to changes in the levels of the encoded protein (e.g. microRNAs). Epigenetic patterns are both plastic, especially during development and cell differentiation when they undergo dynamic changes, and stable, allowing cellular identify to be maintained during mitotic cell divisions. Furthermore, epigenetic changes occur in response to environmental factors including diet, exercise and smoking, and during aging, leading to the suggestion that a possible mechanism for the late onset of common human diseases is the age-related loss of normal epigenetic control. Several studies have indicated that epigenetic changes contribute to the alterations in gene expression and phenotype observed during aging and in OA. The majority of these studies have been performed in cartilage due to its lack of cell heterogeneity, and in the case of DNA methylation, have concentrated on the promoter regions of genes that are dysregulated in OA. In this talk, I will begin by giving an overview of the age- and OA-related epigenetic changes observed in musculoskeletal tissues. I will then present the findings from our recent genome-wide methylation analysis of aged and osteoarthritic cartilage. I will finish by discussing areas for future research into epigenetics and aging of the musculoskeletal system, and in particular, given that OA is a disease of the whole joint, the potential to extend these analyses to other joint tissues.

I-5
UPDATE ON CRYSTALS AND OA

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Calcium-containing crystals including calcium pyrophosphate (CPP) and basic calcium phosphate (BCP) crystals are common components of osteoarthritic (OA) synovial fluid. Similarly, histologic examination of tissue from unselected patients undergoing total joint replacement for OA demonstrate BCP crystal deposition in 100% and CPP crystals in 20-30%. Despite their high prevalence, the role of these crystals in OA remains poorly understood.
New findings relevant to our understanding of crystal formation and the pathogenesis of OA will be discussed. For example, the role of extracellular ATP in OA and crystal formation, the critical participation of ANK protein in cartilage calcification, and some novel work on formation and release of articular cartilage vesicles will be presented. The impact of these studies on available and emerging management strategies will be addressed. The cause/effect relationship between OA and calcium-containing crystal deposition is complex and multifactorial. While many risk factors and some etiologic factors are shared, it is clear that calcium-containing crystals contribute to cartilage damage in OA. CPP crystals produce articular inflammation likely by stimulating components of the innate immune system. The inflammatory potential of BCP crystals as well as the mechanisms involved are much less well understood. These pathways will be discussed in the context of the increasing evidence that inflammatory processes play a critical role in OA. BCP and CPP crystals also produce non-inflammatory tissue damage by directly interacting with synovial cells and chondrocytes, and their presence causes alterations in tissue mechanics which can contribute to joint dysfunction and pain.
Improved recognition of these crystals in the clinical setting and better appreciation of their etiological role in OA will ultimately result in better treatments for all patients with degenerative arthritis.

I-6
CYTOKINE CROSSTALK IN INFLAMMATORY AND MECHANICAL STRESS MECHANISMS IN OSTEOARTHRITIS

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Osteoarthritis (OA) is a whole joint disease, in which thinning and loss of cartilage is a critical determinant in OA progression. The disruption of cartilage homeostasis due to multiple potential causes, related to aging, genetic susceptibility, trauma, or disordered metabolism, is associated with profound phenotypic modifications of chondrocytes. Early changes involve disruption of the pericellular matrix through signaling events mediated by chondrocyte receptors such as discoidin domain receptor-2 (DDR-2). Studies in my laboratory address the mechanisms of gene regulation by which stress- and inflammation-induced signals induce expression of matrix metalloproteinase 13 (MMP-13), the pivotal collagen-degrading proteinase that marks OA progression, as well as other catabolic and inflammatory responses in cartilage and other joint tissues. Common mediators of these processes, which are also involved in mechanotransduction in OA cartilage, include IKKs and MAPKs. These pathways converge on transcriptional regulation by NF-κB, Elf3, C/EBPβ, Runx2, and hypoxia-inducible factor (HIF) 2α. The IKKβ-driven canonical NF-κB signaling pathway coordinates mechanical, inflammatory, and oxidative stress-activated events leading normal chondrocytes to become activated, promoting catabolic events. IKKα, the non-canonical IKK that also participates in canonical signaling, functions as a positive mediator chondrocyte differentiation to a hypertrophic-like phenotype independent of its kinase activity. NF-κB signaling is among the gene signatures in post-traumatic OA and aging models and human OA chondrocytes exhibit prominent epigenomic alterations, such as de-methylation of CpG sites in the promoters of MMP13, IL1B, and other key genes. These alterations lead to de-regulated gene expression, exacerbated, and sustained NF-κB activation and production of proteinases and inflammatory mediators, all of which can be modeled in vitro by IL-1β stimulation. We are currently profiling temporal and spatial changes in gene expression and microRNAs over the course of disease initiation and progression in mouse models of OA using novel mouse strains with inducible, cartilage-specific deletion of IKKα and IKKβ, in addition to the Runx2+/- mouse, which is protected from OA, and the Col11a1+/- chondrodysplasia mouse that develops accelerated OA with aging. We have also generated novel mouse strains